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EDITORIAL REVIEW

Complications of total parenteral nutrition

Continued technological improvements in the quality of nutritional formulations and techniques for parenteral administration have resulted in a major improvement in patient care. The ability to provide all necessary nutrients by intravenous infusion, so-called *total parenteral nutrition* (TPN), has sustained life and growth in patients who otherwise would have died. Most adult patients who derive benefit from this procedure are those with disorders in which alimentary dysfunction precludes adequate nutrition to either save life or prevent serious disease. Included among these disorders are various forms of carcinoma of the gastrointestinal tract, esophageal stricture or stenosis, intestinal fistulae, severe pancreatitis, and the "short-bowel" syndrome. Perhaps one of its advantages has been to re-establish adequate nutritional vitality to patients who suffered life-threatening malnutrition and weight loss and who, following TPN, could undergo corrective surgical procedures.

The purpose of this editorial review is to discuss several interesting and sometimes preventable complications that result from the use of TPN and, in addition, to point out several situations in which TPN used too enthusiastically might directly result in death. This will not be a comprehensive review of all complications one may encounter in patients undergoing TPN. Rather, emphasis will be placed on certain electrolyte disturbances, with special emphasis on phosphate deficiency and its resulting problems. Although infection, oxalosis, disturbances of carbohydrate and lipid metabolism and the potentially important disorders related to carnitine deficiency are of critical importance in patients undergoing TPN, they will not be reviewed in this editorial.

The history of TPN has amusing as well as interesting facets. About 300 years ago, Sir Christopher Wren administered a mixture of ale, opium, and beer intravenously to animals. His intravenous set was a pig bladder and his needle was a quill from a feather [1]. His work may have unintentionally represented the pioneer effort in intravenous substance abuse. More seriously, it appears that the advent of modern TPN therapy began during World War II. A fascinating review describing treatment of starvation based on sound physiological and biochemical principles appeared in 1945 [2]. Participants at this conference detailed a number of interesting observations on prisoners of war subjected to protracted starvation. They pointed out that under such conditions, the bowel underwent atrophy to the extent that it seemed to consist of only its serous coat. This was probably the derivation of the term "cellophane bowel" applied to this condition in the modern literature. Those investigators recognized clearly that under such conditions the intestine would not tolerate food administered by mouth. Almost any food acted as an irritant, causing diarrhea and dehydration. They correctly assumed and showed that administration of nutrients intravenously for several days would apparently permit sufficient functional reconstitution of the gut so that oral administration of food could be tolerated. Our current knowledge that intestinal mucosal cells can repopulate themselves very rapidly corresponds to those earlier observations.

Studies conducted in 1913 by Henriques and Anderson [3] demonstrated that nitrogen equilibrium could be achieved by administering hydrolysates prepared from pancreatic extracts of goat muscle. Before the end of World War II, hydrolysates of known amino acid composition were prepared from proteins digested in proteolytic enzymes derived from pork pancreas, papain, or by simple hydrolysis in sulphuric acid [4]. It was clearly recognized at that time that the drawback of sulphuric acid hydrolysis was its destruction of tryptophane. Amino acid solutions prepared by these techniques were successfully administered to many starved people. The most successful technique appeared to be intravenous administration of protein hydrolysate preparations for 1 to 3 days followed by oral ingestion of small quantities of a solution prepared from dried milk powder, glucose, and vitamins [5, 6]. Interest in TPN was rekindled in 1968 when Dudrick, Wilmore, Vars, and Rhoads [7] showed that by this technique, normal growth and development could be maintained in children for long periods of time.

Role of TPN in acute renal failure

Germane to the interests of this Journal's readers are the questions of whether or not TPN decreases morbidity or whether TPN accelerates recovery of renal function in patients with established acute renal failure. In such patients, especially those in whom acute renal failure resulted from trauma, sepsis or serious systemic disease, catabolism may be pronounced. Indeed, although great advances have been made in techniques of hemodialysis and other measures such as antibiotic therapy, mortality associated with post-traumatic acute renal failure has not changed appreciably since the experience of the Korean War. There is an old principle claiming that catabolism is inevitable in such patients. Accordingly, a person so inflicted should be expected to lose 0.5 kg of body weight per day during the period of oliguria. Thus, any measures that could counteract this "inevitable" catabolic state would be useful in the management of patients with acute renal failure. In an affirmative response to the first question, a number of investigators [8–12] showed that restricted quantities of high quality protein administered with large amounts of nonprotein calories could reduce net urea production, indicating that protein economy could be

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improved in such patients. The administration of such diets in conjunction with appropriate quantities of water and electrolytes not only reduced the usual rate at which azotemia progressed, it also reduced the intensity of acidosis and hyperkalemia, but, of great importance, it reduced the inanition otherwise expected. Nevertheless, similar to some patients with cancer [13], the salutory effects of TPN may be limited greatly in some patients who are desperately ill and markedly catabolic.

The evidence for claims that TPN accelerates recovery from acute renal failure is much more tenuous. Abel et al [14] and Abel [15] were the first to suggest that TPN improved survival and accelerated recovery of renal function in patients with acute renal failure. They compared one patient group who received a solution containing both 50% glucose and essential amino acids to another who received only 50% glucose. Provision of amino acids enhanced survival from 44 to 75%. This work has been criticized by Wesson, Mitch, and Wilmore [16] who pointed out that the patients studied were selected with bias because they represented only 53 of 150 referred for TPN. The others were excluded because of pre-existing renal failure, renal trauma, renal arterial emboli, or because of shock or sepsis.

In another study, Baek et al [17] reported significantly improved survival in 129 patients by the use of a fibrin hydrolysate in addition to glucose infusions. On the other hand, Freund, Harmian, and Fischer [18] described a mortality rate of 91% in 22 patients who received a mixture of essential and nonessential amino acids plus 50% glucose, which are results directly opposite from those of the other investigators. Leonard, Luke, and Siegel [19] and Sofio and Nicora [20] also failed to confirm the salutory effects of essential amino acid administration to patients with acute renal failure.

Feinstein et al [21] studied 30 critically ill patients with acute renal failure who required TPN. Seven received hypertonic glucose, 11 received glucose plus 21 g per day of essential amino acids and 12 received glucose plus 21 g of essential and 21 g of nonessential amino acids per day. Between these three groups, although urea production was less, neither survival nor time of resolution of acute renal failure was significantly different. Wesson, Mitch, and Wilmore [16] summarized the results of all of these studies in detail and conclude that amino acid infusion usually results in a decrease in net urea production but no consistent improvement in the rate of recovery of renal function, at least as assessed by creatinine clearance. Although there is a suggestion that survival of the episode of acute renal failure is improved by such treatment, overall hospital survival is not affected. Despite improvement in nutritional status, such patients continue to die from infection or the nonrenal complications of the condition that caused acute renal failure initially.

Although common sense tells us that providing optimal nutrition for such patients is undoubtedly good, sometimes the associated trauma and tissue destruction are so overwhelming that TPN may not enhance survival. There are also instances of acute renal failure in which TPN may not be necessary, or even justifiable, in terms of expense or potential complications: for example, patients who have incurred acute renal failure as a result of a transfusion reaction and may require no more than simple conservative management.

Mineral and electrolyte disturbances of TPN

Hypokalemia. Hypokalemia occurs commonly in patients undergoing TPN. It does not necessarily reflect potassium deficiency. Thus, TPN solutions contain large amounts of glucose and amino acids that both stimulate release of insulin, or alternatively, crystalline insulin is commonly added to TPN solutions [22]. The mechanism whereby insulin induces hypokalemia is not clearly understood. However, Moore [23] has published observations suggesting that insulin increases sodium permeability of skeletal muscle cells and presumably other tissues, and in turn, the increased sodium concentration in the cytosol activates the magnesium-dependent, Na, K-ATPase. As sodium is thus transported from the cell, electronegativity is generated which in turn promotes the inward movement of potassium ions from the extracellular fluid. Other influences commonly observed in acutely ill patients undergoing TPN could also be responsible for hypokalemia in the absence of total body potassium depletion. For example, hyperventilation with respiratory alkalosis also promotes the cellular uptake of potassium ions. Evidence obtained in vitro suggests that reduction of intracellular hydrogen ion concentration (increased pH) reduces passive outward permeability of potassium ions without producing a comparable reduction on the passive inward permeability [24]. The net effect is the translocation of potassium from extracellular to intracellular fluid. It has also been observed that catecholamine levels may be elevated in patients who are acutely ill. Administration of epinephrine or certain synthetic β-adrenergic agonists, especially those with a selective effect on β-2 adrenergic receptors, promote cellular uptake of potassium ions in muscle and liver [25]. This process appears to depend on increasing the inward sodium leak, cyclic AMP activation, increased Na,K ATPase activity, increased negativity of the membrane potential and passive inward movement of potassium ions. This process can be attenuated by either nonselective β-blockers [26] or increased α-adrenergic activity [27].

Potassium requirements in a normal adult are approximately 0.35 to 0.5 mEq K/kg body wt/day. Requirements may increase to 0.75 to 1.0 mEq/kg body wt during rapid accretion of muscle tissue. To maintain normal tissue composition, about 2.5 to 3.0 mEq of K will be retained for each gram of nitrogen formed as protein. In patients who demonstrate a sharp anabolic response to TPN, potassium deficiency may develop as a result of protoplasm synthesis that outstrips the availability of potassium ions. This response tends to occur several days to 2 weeks or more after TPN has been initiated. More immediate causes of potassium deficiency include diarrhea or losses into the urine. Accelerated renal excretion of potassium ions could occur in patients who also have metabolic alkalosis as the result of loss of gastric contents, or in patients receiving steroids or diuretics. The glycosuria that occurs in patients undergoing TPN is commonly of sufficient magnitude to induce loss of potassium into the urine.

Hypomagnesemia. Normal persons require 0.3 to 0.35 mEq of magnesium/kg/day to maintain a positive magnesium balance. Balance studies in patients on TPN indicate that about 0.5 mEq of magnesium is retained for each gram of nitrogen. These values indicate that magnesium requirements are substantial in

such patients and in most cases explain the development of hypomagnesemia during a course of TPN.

In patients with serious gastrointestinal disease, especially if complicated by steatorrhea, magnesium deficiency often exists before initiation of TPN. The mechanisms of magnesium malabsorption, factors promoting renal loss of magnesium and the fact that magnesium deficiency can cause serious hypocalcemia, potassium deficiency, and phosphorus deficiency are well known. Magnesium deficiency has been implicated as a cause of hypokalemia that resists correction by potassium supplements [28] or hypocalcemia that is not explained by hypoalbuminemia [29]. A patient receiving TPN who becomes weak, who develops myoclonus, muscular fasciculations, athetosis or frank tetany, should be considered to be magnesium deficient until proven otherwise. In patients who have become hypokalemic and hypocalcemic as a result of magnesium deficiency, the extent of magnesium deficiency is usually in excess of 250 or 300 mEq [30]. Slight or modest degrees of hypomagnesemia may occur with deficits as small as 30 to 100 mEq. Slight or modest degrees of hypomagnesemia may also occur in the absence of magnesium deficiency. Studies by Flink et al [31] suggest that in some of these cases, hypomagnesemia may be spurious, reflecting in vitro precipitation of magnesium-fatty acid salt as a result of the fatty acid mobilization induced by high levels of catecholamines. Experimentally, it has been shown that administration of catecholamines causes a reduction of serum magnesium concentrations [32]. Studies of Flink et al [31] showed that administration of nicotinamide prevented mobilization of fatty acids in response to catecholamines, and at the same time prevented hypomagnesemia. Maintenance of normal magnesium stores has been shown to be a critical determinant in protein synthesis and accordingly, nitrogen retention and synthesis of protoplasm will occur at reduced rates in patients who are magnesium-depleted [33].

Phosphorus deficiency and hypophosphatemia. Hypophosphatemia and phosphorus deficiency are common and important complications of TPN. Similar to those deficiency states described previously, phosphorus deficiency may exist in the absence of hypophosphatemia [34]. For example, it is known that in chronic acidosis, intracellular phosphate stores may be decreased but hypophosphatemia does not always occur. A good example of this phenomenon is untreated diabetic ketoacidosis [35]. It is noteworthy that many chronic alcoholics are severely phosphorus deficient. Nevertheless, they may not become hypophosphatemic until the inorganic phosphate in their extracellular fluid is driven into their cells by means of either respiratory alkalosis or the anabolic response that occurs following administration of either amino acids or glucose [36]. Ethanol administered chronically to dogs in intoxicating quantities results in a decrease of muscle phosphorus content to a level quantitatively similar to that observed in alcoholic patients [37]. Even though muscle becomes phosphorus deficient, serum phosphorus concentration usually remains normal. The mechanism whereby ethanol causes muscle cells to lose phosphorus has not been elucidated.

Any condition that lowers intracellular pH will simultaneously reduce the activity of phosphofructokinase [38]. This results in decreased phosphorylation, liberation of free phosphate ions into the extracellular fluid and excretion of phosphate into the urine. A sudden correction of acidosis, or alternatively, a sudden appearance of the anabolic state will increase phosphorylation and consumption of extracellular phosphate so that hypophosphatemia appears [39].

Substantial weight loss as the result of poor food intake does not ordinarily cause a marked reduction in the total quantity of phosphorus in muscle tissue if phosphorus content is indexed in terms of tissue protein [40]. Under such conditions, while cellular composition measurements might show slight elevations of sodium, chloride and water content and perhaps slight decrements of phosphorus and potassium content, severe disturbances are usually not seen. It seems as if cells simply undergo atrophy and in the process manage to maintain a fairly normal composition of elements. When such a patient is begun on TPN, provided their cells are capable of an anabolic response, rebuilding of protoplasm will begin. If all nutrients are provided in ideal quantities, derangements of cellular composition and plasma composition will usually not occur [41]. On the other hand, if phosphorus is relatively deficient, phosphorus deficiency and hypophosphatemia will slowly appear [42]. A person might be given appropriate quantities of essential amino acids, calories in the form of both glucose and fat, vitamins, trace minerals and all elements except, for example, one third the required amount of phosphorus. As protoplasm is synthesized with inadequate supplies of phosphorus, phosphorus will virtually disappear from the urine, serum phosphorus will fall and frank symptoms of hypophosphatemia and phosphorus depletion will appear in perhaps 1 to 3 weeks. Under such conditions, the most prominent manifestations of phosphorus deficiency may be related to central nervous system dysfunction [43]. Various observers have described irritability, apprehension, muscular weakness, numbness, parathesias, dysarthria, dysphagia, inability to swallow secretions, anisocoria, unreactive dilated pupils, nystagmus, diplopia, patchy visual field defects in color perception, ptosis, confusion, obtundation, ballismus, convulsive seizures, coma, and death [43–53]. Because such patients may be profoundly depleted of phosphorus, red cell contents of 2,3-diphosphoglycerate (2,3-DPG) and ATP may be severely depressed [43]. Since both of these compounds promote the release of oxygen from hemoglobin, tissue hypoxia is thought to occur and is held responsible for a great deal of the central nervous system manifestations. Thus, Travis et al [43] showed that under such conditions, electroencephalographic abnormalities could be related to the depression of red cell 2,3-DPG. The abnormally low 2,3-DPG and central nervous system dysfunction responded favorably to phosphate replacement and correction of hypophosphatemia. Clearly, such symptoms do not appear in patients undergoing TPN who are not allowed to become phosphorus depleted and hypophosphatemic. Nevertheless, it seems possible that tissue hypoxia is not the only abnormality in these patients since at the prevailing levels of serum phosphorus concentration (below 0.5 to 1.0 mg/dl), it is quite likely that tissue phosphorylation and utilization of glucose by the brain would be markedly impaired. Studies to examine the latter possibility have not yet been performed.

Muscle cell dysfunction and rhabdomyolysis may also occur in patients who become severely phosphorus depleted and hypophosphatemic [34, 40, 54]. However, the incidence of this complication in the setting of TPN has proven to be rare. Most

cases of hypophosphatemic rhabdomyolysis have occurred in patients with alcoholism who are severely phosphorus deficient before hypophosphatemia is induced by other means [34, 54]. Clinical observations [54] and experimental studies [40] suggest that rhabdomyolysis does not occur with hypophosphatemia unless muscle cell injury pre-exists. It was shown that phosphorus deficiency in the absence of hypophosphatemia induced a subclinical biochemical injury of the muscle cells [55]. If acute hypophosphatemia was then induced by hyperalimentation, frank rhabdomyolysis followed [40]. Provision of phosphorus in adequate quantities to prevent acute hypophosphatemia under such conditions prevents rhabdomyolysis. In contrast, if a dog is underfed with an otherwise balanced diet so that derangements of cellular composition do not occur, TPN-induced hypophosphatemia does not appear to cause injury to muscle cells [56]. Such observations appear to bear relevance to several clinical observations. First, acute rhabdomyolysis is exceptionally rare in patients who have simply lost weight because of decreased food intake although hypophosphatemia might appear over the course of days to weeks. In such patients, muscle phosphorus content was probably normal before initiation of TPN. Similarly, acute rhabdomyolysis is exceptionally rare in patients recovering from diabetic ketoacidosis although they often become hypophosphatemic. Studies have shown that the great majority of patients treated for diabetic ketoacidosis are not phosphorus deficient [39]. Indeed, since diabetic ketoacidosis usually develops over a period of a few days, these patients have not had time to become significantly phosphorus deficient. The induction of acute hypophosphatemia by insulin therapy and correction of metabolic acidosis causes hypophosphatemia but in the absence of pre-existent muscle cell injury, it seldom results in significant rhabdomyolysis.

A number of clinical reports have described patients treated with TPN who have developed acute hypophosphatemia associated with respiratory failure [46, 48, 49, 51–53, 57–59]. A number of these patients have become seriously ill from respiratory acidosis and hypoxia. Most were desperately ill and in intensive care unit settings; some were also receiving large amounts of glucose or amino acids intravenously. Some of the patients demonstrated abnormalities of central nervous system function or peripheral neuropathy, profound weakness, and muscle paralysis before the appearance of diaphragm failure. Although ascending paralysis may suggest the Guillain-Barré syndrome, the cerebrospinal fluid is usually normal.

Nearly all patients who have developed acute respiratory failure during TPN have had pre-existing conditions that would be expected to cause abnormalities of muscle cell ion transport and element composition. Reported instances of this interesting phenomenon have occurred in patients with chronic intestinal fistulae, malabsorption syndrome, Crohn disease, ulcerative colitis, small bowel resection, exocrine pancreatic insufficiency, chronic alcoholism associated with malnutrition, and gastrointestinal cancer. In each instance, serum phosphorus concentrations have been less than 1.0 mg/dl. In some cases, the patients were also hypokalemic. However, as in the report of Newman, Neff, and Ziporin [57, 58], respiratory failure persisted despite the correction of hypokalemia, apparently responding to subsequent administration of phosphate salts and correction of hypophosphatemia. Experimental studies on phosphorus deficient dogs have also shown diminished diaphragm function as a result of muscular weakness [60].

The incidence of rhabdomyolysis in patients with respiratory failure and muscular paralysis is difficult to ascertain since muscle enzyme data are missing from nearly all reports. In agreement with the cases described by Newman, Neff, and Ziporin [57, 58] in which CPK values were normal, rhabdomyolysis in this setting, I suspect, is usually absent or mild. This speculation is based on the fact that serum phosphorus in such patients remains profoundly depressed day after day and does not follow the usual course of spontaneous correction as ordinarily seen in rhabdomyolysis. That serum phosphorus may be within normal limits or even elevated in the presence of rhabdomyolysis induced by phosphorus depletion and hypophosphatemia has been recognized in both human [54] and animal [40] studies. In such instances, the initial hypophosphatemia is often missed, and it is assumed that the residual phosphorus content of skeletal muscle is released in sufficient quantities to correct the pre-existent hypophosphatemia. In fact, in our previously reported clinical studies [54], the serum phosphorus concentration was higher and the muscle phosphorus content lower in those patients with the greatest clinical degree of rhabdomyolysis. The "masking" of phosphorus deficiency as the cause of muscle injury in such instances might also explain the report by Stewart and Hensley [61], who described acute rhabdomyolysis during the course of TPN in a patient with long standing celiac disease and esophageal carcinoma.

It should be kept in mind that TPN-associated respiratory failure is not always the result of hypophosphatemia. Covelli et al [62] described three patients who developed respiratory acidosis during the course of TPN that was not apparently associated with hypophosphatemia or other recognizable element disturbance. In these patients, ventilatory capacity was not sufficient to remove carbon dioxide produced by metabolism of nutrients provided in the TPN solutions. Either increasing the volume of ventilation or if that is not possible, reducing the total amount of calories provided would reduce the P_{CO_2} and improve the carbon dioxide-induced narcosis and acidosis [63]. Although most patients are capable of increasing their ventilatory rate to effect removal of carbon dioxide produced by metabolism, it is well known that patients who are debilitated or starved show depression of the hypoxic ventilatory response [64, 65].

Acid-base disorders. A variety of acid-base derangements may be seen in patients treated by TPN. In a number of these instances, the particular acid-base disturbance is the result of the patient's primary disease. For example, patients with bacteremia and sepsis may develop severe respiratory alkalosis as a result of hyperventilation [66]. Indeed, the appearance of respiratory alkalosis with its characteristic depression of cerebral blood flow [67] and resulting mental confusion may be one of the first clues that sepsis exists.

Although metabolic alkalosis most commonly results from potassium deficiency or loss of gastric contents due to vomiting or aspiration, one should realize that it may also appear rather suddenly in patients who receive glucose following a period of starvation, so-called "refeeding alkalosis" [68]. Several factors are thought to be responsible for this interesting phenomenon. They include *(1)* an increased renal bicarbonate reabsorptive

capacity which occurs as a direct result of fasting, *(2)* a further increment in this parameter subsequent to the ingestion of glucose, and *(3)* generation of new bicarbonate as a result of metabolizing ketone bodies to bicarbonate and excretion of net acid by the kidney. Studies by Stinebaugh and Schloeder [68] showed that patients were in positive sodium chloride balance before alkalosis was induced by refeeding, thus excluding volume depletion or chloride deficiency as a hypothetical cause for this phenomenon.

Acute metabolic acidosis in patients undergoing TPN may occur for several reasons, for example, excessive losses of alkaline secretions from the pancreas or net bicarbonate loss from diarrhea. Metabolic acidosis with a high anion gap might also reflect the presence of uremia. Lactic acidosis may be a cause in patients who have congestive heart failure, hypoxia, or those who perfuse their peripheral tissues poorly because of volume depletion. Phosphorus deficiency and hypophosphatemia may impair renal excretion of acid.

Hyperchloremic metabolic acidosis may occur as a complication of TPN therapy with synthetic amino acid preparations, but it has not been observed in patients who receive casein or fibrin hydrolysates [69]. Studies on infants receiving these preparations have excluded loss of base from the gastrointestinal tract or acidification defects by the kidney. Chan [70] measured the basal endogenous acid balance in infants receiving 20% glucose and compared these to acid production and excretion during infusions of synthetic amino acids and casein hydrolysate. Net acid production tended to be higher in those infants receiving the synthetic amino acid solution. This could not be attributed to either the pH of the solutions administered or their content of titratable acidity [71]. Heird et al [69] showed very clearly that the specific amino acid composition of the solutions prepared from synthetic amino acids would result in hyperchloremic metabolic acidosis if the solution contained a disproportionate quantity of the cationic amino acids histidine, arginine, or lysine. When metabolized, these amino acids yield net hydrogen ion production. Originally, the chloride salts of these amino acids were used; consequently, the end product of their metabolism would be hydrochloric acid. On the other hand, it was shown that if the chloride ion was replaced by acetate, metabolic acidosis did not occur. This was explained by the fact that acetate is metabolized and in the process consumes hydrogen ion thus avoiding metabolic acidosis. To explain the absence of metabolic acidosis when either casein or fibrin hydrolysates were employed to TPN, Heird et al [69] showed that these solutions contained an excess of amino acids carrying a negative charge at pH 7.4, for example, glutamate and aspartate, and uncharacterized anionic peptides, that would not yield excessive hydrogen ions when metabolized.

Severe metabolic acidosis in children treated with TPN for chronic diarrhea and protein calorie malnutrition has been associated with phosphorus deficiency [72], representing one of the most fascinating complications of phosphate depletion. Acid excretion by the kidney depends on the presence of phosphate in the urine, ammonia production, and the secretion of free hydrogen ions by the renal tubule. In this process, Na_2HPO_4 is filtered at the glomerulus. One of the sodium ions is exchanged for a hydrogen ion and the phosphate is excreted as NaH_2O_4. This component of hydrogen ion excretion is measured as titratable acidity. Obviously, in nearly all instances of TPN-induced hypophosphatemia, urinary phosphate concentration becomes essentially zero, thereby eliminating this mechanism of acid excretion. One would surmise that in the absence of phosphate in the urine, the kidney might increase ammonia production so as to increase the capacity of hydrogen ion secretion by formation of ammonium ion (NH_4^+) in the renal tubule. Thus, one would suspect that hydrogen ion concentration would increase in the tubular cell and that this would increase ammonia production. However, it is of interest that cellular pH apparently rises under conditions of phosphate deficiency. Studies directly measuring intracellular pH with the DMO technique [73] in liver and muscle have shown this to be the case. It is assumed that this also happens in the kidney. Presumably, in phosphorus deficiency, because of intracellular alkalosis, total ammonia formation in the kidney decreases. One then must ask, why is metabolic acidosis not a regular event in all patients with phosphorus deficiency? Thus, when two of the major mechanisms to excrete metabolic acid are impaired, how could a normal pH be maintained?

To answer this question, let us consider the normal response to phosphorus deficiency. When phosphorus is removed from the diet, and especially if its depletion is accelerated by ingestion of phosphate-binding antacids, even before serum phosphorus concentration falls, phosphorus is mobilized from the skeleton. Some believe that an unidentified humoral substance is released in response to phosphorus deprivation resulting in mobilization of bone apatite [74]. Bone apatite is composed of calcium, carbonate, phosphorus, and water. The immediate response to phosphorus deprivation is the appearance of hypercalciuria. In the normal adult, mobilization of bone is almost never of sufficient magnitude to result in hypercalcemia. In children, presumably because bone is a more active tissue, phosphorus deprivation is a well recognized cause of both hypercalcemia and hypercalcuria. The implication is that apatite and hence calcium is mobilized so rapidly that its rate of excretion by the kidney is not sufficient to prevent hypercalcemia. In the adult, hypercalcemia does not ordinarily occur unless there exists some disease that increases bone turnover such as hyperparathyroidism, Paget disease, or metastatic cancer of bone. The explanation for the absence of metabolic acidosis in phosphorus deficiency is thus related to the mobilization of carbonate from bone which occurs at a sufficient rate to exactly titrate the hydrogen ions retained by the kidney. Experimental studies by Emmett et al [75] on phosphorus deficient rats show that when an agent such as colchicine is administered to suppress apatite mobilization, metabolic acidosis rapidly appears.

Studies by Booth, Tsia, and Morris [76] on vitamin D deficient chicks suggest that if bone mobilization ordinarily anticipated when phosphorus deficiency is impaired, then metabolic acidosis may occur. This observation seems to coincide with the report of Kohaut et al [72] on malnourished children with diarrhea. Thus, if they had a deficiency state that impaired mobilization of apatite from bone, carbonate would not become available to buffer retained metabolic acid. In those studies, administration of phosphorus lead to a rapid increase of titratable acidity of the urine, ammonia production, and a rapid resolution of metabolic acidosis. In fact, similar to studies on experimental animals [75], hydrogen ion excretion by the kidney and/or mobilization of carbonate from bone occurred at a

sufficiently rapid rate that there was an "overshoot" metabolic alkalosis. Other experimental studies on dogs [73] have reported defective bicarbonate reabsorption by the proximal tubule in severe phosphorus deficiency. This finding could not be confirmed [77, 78]. Another study has shown a mild defect in hydrogen ion secretion and urinary acidification in phosphorus-deprived rats [79].

The cardiovascular system in starvation, TPN, and hypophosphatemia

Cardiovascular events are commonly the mode of death for persons who died as a result of starvation or those who die during a course of refeeding for starvation. Besides being abnormally small, the heart in starvation is soft, pale, and flabby [80]. Likewise, the hearts from prisoners of war who died during the first week of refeeding showed marked brown atrophy, scattered collections of lymphocytes, condensations of nuclei, fatty infiltration, and degeneration of autonomic ganglia.

The cardiovascular system in starving persons rescued from prisoner of war camps who died as a result of the "refeeding syndrome" is no different from that seen in patients encountered today with anorexia nervosa or other conditions resulting from longstanding inanition and malnutrition. Considering the severely limited cardiac reserve, one can easily predict the calamitous cardiac outcome of administering excessively large volumes of solutions composed of hypertonic glucose and amino acids [81].

Besides clinical evidence for limited cardiac reserve in cachectic patients [82], substantial evidence suggests that phosphorus deficiency and hypophosphatemia also exert adverse effects on ventricular contractility. O'Connor, Wheeler, and Bethune [83] showed improvement in left ventricular performance in patients following treatment for hypophosphatemia. Experimental studies by Fuller et al [84] clearly showed evidence of depressed myocardial performance in phosphorus-deficient dogs that improved after repletion. Moreover, Brautbar et al reported abnormalities in energy production [85] and lipid metabolism in phosphorus deficient rates [86].

Finally, it is well known that hypophosphatemia occurs during nutrition therapy in patients with anorexia nervosa [87, 88]. Thus, physicians who treat patients with severe malnutrition or anorexia nervosa should be aware that the acute administration of large quantities of calories and large volumes of fluids to such patients is an unwise therapeutic decision. There is no need to hurry. In my view, the ideal method for administering nutrients to poorly nourished patients, especially those typified by advanced anorexia nervosa, is to begin slowly, with perhaps 300 to 400 calories on the first day, and to increase the total number of calories administered per day gradually while carefully monitoring the patient, both physically and chemically, in order to avoid problems with hypervolemia, electrolyte disturbances, or acidosis.

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